K110215

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510(k) Summary

CONFIRM anti-Estrogen Receptor (SP1) Rabbit Monoclonal Primary Antibody

This summary of 510(k) safety and effectiveness information is being submitted in accordance with the requirements of 21 CFR 807.92.

Submitter Name:	Ventana Medical Systems, Inc
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Date Summary was Prepared: December 14, 2012

DEVICE

Trade Name: CONFIRM anti-Estrogen Receptor (SP1) Rabbit Monoclonal Primary Antibody
Common Name: CONFIRM anti-ER (SP1)
Classification Name: Immunohistochemistry Antibody Assay, Estrogen Receptor

PREDICATE DEVICE

FLEX Monoclonal Rabbit Anti-Human Estrogen Receptor α Clone SP1 (K081286)

DEVICE DESCRIPTION

CONFIRM anti-ER (SP1) binds to human estrogen receptor alpha (ER) in paraffin embedded tissue sections. The antibody is diluted in 0.05 M Tris-HCl with 2% carrier protein, and 0.10% ProClin 300, a preservative. There is trace (~0.2%) fetal calf serum of U.S. origin from the stock solution. Total protein concentration of the reagent is approximately 20 mg/mL. Specific antibody concentration is approximately 1 µg/mL. CONFIRM anti-ER (SP1) is a rabbit monoclonal antibody produced as a cell culture supernatant.

CONFIRM anti-ER (SP1) is optimized for use on the BenchMark XT and BenchMark ULTRA automated slides stainers using iView DAB and *ultra*View DAB detection chemistries.

INTENDED USE

This antibody is intended for in vitro diagnostic (IVD) use.

CONFIRM anti-Estrogen Receptor (ER) (SP1) Rabbit Monoclonal Primary Antibody is intended for laboratory use for the qualitative detection of estrogen receptor (ER) antigen in sections of formalin-fixed, paraffin-embedded breast tissue on a Ventana automated slide stainer with Ventana detection kits and ancillary reagents. CONFIRM anti-ER (SP1) is directed against an epitope present on human ER alpha protein located in the nucleus of ER positive normal and neoplastic cells. CONFIRM anti-ER (SP1) is indicated as an aid in the management, prognosis, and prediction of hormone therapy for breast carcinoma.

This product should be interpreted by a qualified pathologist in conjunction with histological examination, relevant clinical information, and proper controls.

Prescription use only.

TECHNOLOGICAL CHARACTERISTICS

The CONFIRM anti-ER (SP1) product and the predicate FLEX Monoclonal Rabbit Anti-Human Estrogen Receptor α Clone SP1 product utilize the same rabbit monoclonal antibody clone (SP1) which recognizes human estrogen receptor alpha. A synthetic peptide corresponding to the C-terminal portion of the ER molecule was used as the immunogen to generate the clone. The SP1 clone has been shown to react with 66 kD protein from MCF-7 cells via Western blotting. The protein size is in agreement with that predicted from the cloning of the gene for ER.

The CONFIRM anti-ER (SP1) has the same technological characteristics as the predicate device. Both products specifically bind to estrogen receptor proteins located in the nuclei of cells, and are optimized for use on formalin-fixed paraffin embedded tissues. Both products are optimized for use on automated slide stainers using similar detection chemistry principles. Both aid in the prognosis of breast carcinoma.

METHOD COMPARISON

A randomized, multi-site, multi-reader study was conducted to compare the staining performance of the CONFIRM anti-ER (SP1) on the BenchMark ULTRA instrument versus the BenchMark XT instrument. One hundred twenty (120) ER negative and 132 ER positive cases of breast cancer representing the clinical range of the assay were randomly assigned to three study sites. Each site stained its assigned cases with the CONFIRM anti-ER (SP1) antibody on a BenchMark ULTRA instrument and a CONFIRM anti-ER (SP1) antibody on a BenchMark XT instrument. The stained slides were evaluated by pathologists who determined the percentage of stained tumor cells. A case was considered ER positive if there was staining of the nucleus in at least ≥1% of invasive tumor cells.

In the direct comparison of CONFIRM anti-ER (SP1) on the BenchMark XT versus the BenchMark ULTRA, the overall percent agreement (OPA) for ER status (positive/negative) was 90.9 (86.2-94.1).

EQUIVALENCE TO PREDICATE

A randomized, single-site, multi-reader study was conducted using a clinical cohort of 820 invasive breast cancer cases comparing the staining performance of CONFIRM anti-ER (SP1) and FLEX anti-ER (SP1) to progression-free survival outcome. Additional comparison was made to the preceding technology ligand binding assay (LBA) data available from the cohort database. Cases were included in the analyses if the patient had a confirmed diagnosis of invasive breast carcinoma and received treatment with primary surgical intervention with or without post-operative local radiation therapy followed by adjuvant tamoxifen endocrine therapy (20 mg p.o./day) for 5 years. Cases were excluded from analyses if diagnostic biopsy or primary surgical tissue specimens were unavailable, if there had been a prior cancer diagnosis (except non-melanoma skin cancer), or if the patient received prior or adjuvant chemotherapy. A total of 1907 tissue microarray cores from 594 breast cancer cases with primary tumor were stained on the BenchMark ULTRA instrument. The stained slides were evaluated by three independent pathologists who determined the percentage of stained tumor cells. A case was considered ER positive if there was staining of the nucleus in at least >1% of invasive tumor cells.

In a direct comparison of CONFIRM anti-ER (SP1) and FLEX anti-ER (SP1) assay results, the OPA for ER status (positive/negative) was 97.8% (95% CI: 96.2–98.8%).

In comparison against patient outcome, the CONFIRM anti-ER (SP1) assay and FLEX anti-ER (SP1) assay yielded identical median survival times in tamoxifen treated patients (101.6 months in ER+ patients vs 47.2 months in ER- patients). For both assays the log-rank test showed the difference between ER+/ER- relative to survival is statistically significant ($P < 0.001$).

When adjusted for clinical covariates known to influence survival (age, nodal status, tumor size, and tumor grade) the Cox proportional hazard ratio for ER+ compared to ER- in CONFIRM anti-ER (SP1) was 0.469 ($p = 0.026$), while in FLEX anti-ER (SP1) it was 0.564 ($P = 0.083$). Inspection of the point estimates and their confidence intervals show that the two results are essentially identical to each other. The chi-square statistics associated with the likelihood ratio (LR) were (100.395 for Ventana vs 98.951 for Dako).

The CONFIRM anti-ER (SP1) and FLEX anti-ER (SP1) PPA rates were identical for cases that were ER+ by LBA (98.6%; 95% CI: 96.8–99.4%, for both assays). The difference between CONFIRM anti-ER (SP1) and FLEX anti-ER (SP1) (0.0%; 95% CI -1.6-1.6) was not statistically significantly different from zero at the 0.05 level (McNemar's exact test p-value >0.999). The CONFIRM anti-ER (SP1) NPA was lower than the FLEX anti-ER (SP1) NPA with respect to LBA ER status (27.6% vs 34.5%, respectively), but the difference between NPAs (-6.9%; 95% CI: -19.6–5.8%) was not statistically significantly different from zero at the 0.05 significance level (McNemar's exact test p-value = 0.500).

CONCLUSIONS

The CONFIRM anti-Estrogen Receptor (SP1) Rabbit Monoclonal Primary Antibody is substantially equivalent to the predicate FLEX Monoclonal Rabbit Anti-Human Estrogen Receptor α Clone SP1 based on their intended use and technological characteristics. In performance comparison to preceding technology (ligand binding assay) and effectiveness at predicting patient outcome for hormone therapy the assays were substantially equivalent.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
Document Control Center – WO66-G609
Silver Spring, MD 20993-002

December 17, 2012

Ventana Medical Systems, Inc.
c/o Ms. Roxane Bonner
1910 E. Innovations Park Drive
Tucson, AZ 85755

Re: k110215
Trade/Device Name: CONFIRM Anti-Estrogen Receptor (SP1) Rabbit Monoclonal Antibody
Regulation Number: 21 CFR 864.1860
Regulation Name: Immunohistochemistry reagents and kits
Regulatory Class: Class II
Product Codes: MYA
Dated: November 23, 2012
Received: November 26, 2012

Dear Ms. Bonner:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act.. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration.

If your device is classified (see above) into class II (Special Controls), it may be subject to such additional controls. Existing major regulations affecting your device can be found in Title 21, Code of Federal Regulations (CFR), Parts 800 to 895. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Parts 801 and 809); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803); and good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820). This letter will allow you to begin marketing your device as described in your Section 510(k) premarket notification. The FDA finding of substantial equivalence of your device to a legally marketed

predicate device results in a classification for your device and thus, permits your device to proceed to the market.

If you desire specific advice for your device on our labeling regulation (21 CFR Parts 801 and 809), please contact the Office of *In Vitro* Diagnostics and Radiological Health at (301) 796-5450. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm for the CDRH's Office of Surveillance and Biometrics/Division of Postmarket Surveillance.

You may obtain other general information on your responsibilities under the Act from the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638-2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/cdrh/industry/support/index.html.

Sincerely yours,

Maria M. Chan

Maria M. Chan, Ph.D.
Director
Division of Immunology and Hematology Devices
Office of *In Vitro* Diagnostics and Radiological Health
Center for Devices and Radiological Health

Enclosure

Indications for Use

510(k) Number: K110215

Device Name:

CONFIRM anti-Estrogen Receptor (ER) (SP1) Rabbit Monoclonal Primary Antibody

Indications for Use:

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This product should be interpreted by a qualified pathologist in conjunction with histological examination, relevant clinical information, and proper controls.

Prescription use only.

Prescription Use ___X___ (Part 21 CFR 801 Subpart D)	AND/OR	Over-The-Counter Use _____ (21 CFR 801 Subpart C)

(PLEASE DO NOT WRITE BELOW THIS LINE-CONTINUE ON ANOTHER PAGE OF NEEDED)

Concurrence of CDRH, Office of In Vitro Diagnostic Devices (OIVD)

Division Sign-Off
Office of In Vitro Diagnostic Device
Evaluation and Safety

510(k) K110215